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EXAMINER	
EPPERSON, JON D	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 04/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/756,092	CIMA ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *180-304* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *180-184,186-193,198-200,204,207,228-235,246,249,258,286,295 and 299-304* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/14/03;5/7/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 185,194-197,201-203,205,206,208-227,236-245,247,248,250-257,259-285,287-294 and 296-298.

DETAILED ACTION

Request for Continued Examination (RCE)

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection (e.g., see 4/7/04 Response). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/9/04 has been entered. Applicants canceled all pending claims and added claims 180-304 (e.g., see 4/7/04 Response). Claims 180, 257-275 and 302-304 were also amended via a preliminary amendment (e.g., see 7/9/04 Response). Therefore, claims 180-304 are currently pending. In addition, claims 185, 194-197, 201-203, 205, 206, 208-227, 236-245, 247, 248, 250-257, 259-285, 287-294 and 296-298 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected species (see below i.e., ***Response to Restriction and/or Election of Species***). Therefore, claims 180-184, 186-193, 198-200, 204, 207, 228-235, 246, 249, 258, 286, 295 and 299-304 are examined on the merits.

Those sections of Title 35, US code, not included in the instant action can be found in previous office actions.

Response to Restriction and/or Election of Species

2. Applicant's election of species (e.g., see 1/10/05 Response) is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction

requirement, the election of species has also been treated as an election without traverse (MPEP § 818.03(a) and/ or 37 CFR 1.111(b)).

3. As a result, the restriction requirement and/or election of species is still deemed proper and is therefore made FINAL.

Priority

4. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

This application claims benefit of 60/221,539 (filed 7/28/2000), 60/196,821 (filed 4/13/2000) and 60/175,047 (filed 1/7/2000) and is a CIP of 09/628,667 (filed 7/28/2000) and is a CIP of 09/650,462 (filed 3/31/2000), which claims benefit of 60/127,755 (filed 4/5/1999). However, the applications upon which priority is claimed fail to provide adequate support under 35 U.S.C. § 112 for the claims of this application. Specifically all the provisional applications do not provide support for an automated dispensing apparatus "directed by a work list generated by formulations software, said work list allowing a file to be used as a process command rather than discrete programmed steps" as presented, for example, in independent claims 180 and 302-304. In addition, the CIP applications and their related 60/127,755 provisional application fail to provide adequate support for "sealing" the samples as disclosed, for example, in independent claims 180 and 302-304 and also for the use of a "septum", "syringe", "needle" and/or "septum-piercing method steps" as disclosed in dependent claims 187, 193 and 233 that further limit the "sealing" step. In addition, the Examiner only finds support for Raman spectroscopy as exemplified in claims 189 and 286 of the present application in the 60/196,821 application (filed

4/13/2000). Furthermore, the Examiner only finds support for "integrated modules, or workstations" in 60/196,821 (filed 4/13/2000) as exemplified in independent claims 180 and 302-304. In addition, no support for "evaporating" the solvent as disclosed in claims 192 and 302 can be found. Finally, the Examiner does not find support for a "metal support plate" as exemplified in claim 183 in any of the priority documents. Thus, none of the priority applications provide adequate written support for a method that **combines all of the limitations** that are currently claimed. If applicant believes this to be in error, applicant must disclose where in the specification support for these limitations can be found (i.e., page and line number) and wherein support for a method that uses **all** of these limitations simultaneously can be found in a single priority document. Therefore the filing date of the instant application is deemed to be its actual filing date of ***January 8, 2001***.

Withdrawn Objections/Rejections

5. All previous rejections are withdrawn in view of Applicants' arguments and/or amendments.

New Rejections and/or Objections

Objections to the Claims

6. Claim 186 and 229 are objected to because of the following informalities:

A. Claim 186 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form or rewrite the claim(s) in independent form. Claim 186 depends from

claim 182. Claim 186 recites in part: "generation of a work list." However, claim 187, recites the limitation "a work list generated by formulation software." Therefore, claim 186 does not further limit claim 180.

B. Claims 229 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 188. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claims Rejections - 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 180-184, 186-193, 198-200, 204, 207, 228-235, 246, 249, 258, 286, 295 and 299-304 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. ***Claim 198*** recites the limitation "said grouped samples" in the first line. There is insufficient antecedent basis for this limitation in the claim. Therefore, claim 198 and all dependent claims are rejection under 35 U.S.C. § 112, second paragraph.

B. For ***claim 180 and 302-304***, the term "informatics" in the last line of step (d) is vague and indefinite. For example, it is not clear what methods and/or apparatus and/or computer programs (if any) are encompassed by "informatics"? Although the

specification uses the term to describe hoped for results produced by informatics (e.g., the ability to group crystals into particular families) the specification does not actually state what "informatics" is and/or provide any formal definition for the term. Consequently, the metes and bound of the claimed invention cannot be determined. Therefore, claims 180, 302, 303 and all dependent claims are rejected under 35 U.S.C. § 112, second paragraph.

C. For ***claim 181***, the term "further analysis" in the first line is vague and indefinite. For example, it is not clear what "further analysis" is being required? Conceivably just acknowledgement of the fact that crystals have been produced and/or acquired represents some sort of further "mental" analysis, which would also be an inherent feature of the independent claim. Thus, it is not clear how this further analysis further limits the claim. Consequently, the metes and bound of the claimed invention cannot be determined. Therefore, claim 181 and all dependent claims are rejected under 35 U.S.C. § 112, second paragraph.

D. For ***claim 301***, the term "machine vision technology" is vague and indefinite. For example, it is not clear what would be encompassed by this technology? Applicants provide an example wherein a CCD camera is used in conjunction with different light polarization (e.g., see specification, section 6.5.1), but Applicants do not provide a definition for the term, nor do they state what other techniques would be included in this genus, nor do they state what common features are shared by members of this genus. Consequently, the metes and bound of the claimed invention cannot be determined.

Therefore, claim 301 and all dependent claims are rejected under 35 U.S.C. § 112, second paragraph.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 180-184, 186-193, 198-200, 204, 207, 228-235, 246, 249, 258, 286, 295, 299-304 are rejected under 35 U.S.C. 103(a) as being unpatentable over Galakatos et al. (WO 00/59627) (Date of Patent is **October 12, 2000**) and Merritt (Merritt, A. T. "Uptake of new technology in lead optimization for drug discovery" **1998** DDT, 3(11), 505-510) and Saneii et al. (U.S. Patent No. 5,746,982) (Date of Patent is **May 5, 1998**) and Wang et al. (Wang, T.; Zeng, L.; Strader, T.;

Burton, L.; Kassel, D. B. "A New Ultra-high Throughput Method for Characterizing Combinatorial Libraries Incorporating a Multiple Probe Autosampler Coupled with Flow Injection mass Spectrometry Analysis" *Rapid Commun. mass Spectrom.* **1998** *12*, 1123-1129) and Newsam et al. (Newsam, J. M.; Schuth, F. "Combinatorial Approaches As a component of High-Throughput Experimentation (THE) in Catalysis Research" Biotechnology and Bioengineering (Combinatorial Chemistry) **1999**, 61(4), 203-216).

For ***claim 180 and 302-304***, Galakatos et al. (see entire document) teach methods for the use of high throughput combinatorial formulation technologies (e.g., see abstract), which read on the claimed invention. For example, Galakatos et al. teach the formation of an array (e.g., see claim 22, "formulating the materials into an array of multiple formulations located at separate sites or in separate wells"). In addition, Galakatos et al. teach at least 96 samples (e.g., see page 6, paragraph 1, "'High throughput' refers to the number of samples generated or screened ... preferably more than 1000 samples"). In addition, Galakatos et al. disclose using an automated dispensing apparatus directed by a work list generated by formulation software, said work list allowing a file to be used as a process command rather than discrete programmed steps (e.g., see Galakatos, page 23, paragraph 1, "There are basically two types of Informatics that can be used ... referring to automated solid or liquid dispensing system and data output, respectively. One is system automation and control software that enables the integrated set of manipulations to occur and track the process flow ... A second is scientific derivatization which collects and stores data to enable further development and design of formulations, including identification of complex interactions between the actives and excipients ... The data can

then be processed so as to optimize the ability of scientific personnel to conduct future experiments to optimize the formulations"; see also figure 2). Galakatos also disclose the generation of a less than 100 milligrams of a small molecule pharmaceutical (e.g., see background of the invention, "This invention is generally in the field of methods and systems for developing optimized formulations for ... pharmaceutical formulations"; see also lines bridging pages 5-6, "In a more preferred embodiment, the samples consist of less than 25 micrograms"). In addition, each sample differs by at least one of (i) the amount or concentration of the small molecule pharmaceutical, (ii) the identity of one or more of a solvent, acid or base; or (iii) an amount or concentration of none or more of a solvent, acid or base (e.g., see page, 6, last paragraph, "In the preferred embodiment, the libraries are constructed using systematic combinations of two or more components, for example, by varying concentrations of drug and selection and concentration of one or more excipients, as demonstrated in the following examples, in a grid or array (i. e., an ordered set of components) such as a 96 well plate, nano or microarray"). In addition, Galakatos et al. disclose processing said samples by heating/cooling samples (e.g., see page 17, last paragraph, "In a preferred embodiment to select optimal drug formulations for oral delivery, a system assays formulations based on physical parameters ... Physical parameters include ... microstructure ... Microstructures includes crystalline or amorphous structures, or combinations thereof, polymorphs ... Crystallinity variants can be produced by changing ... heating ... quench cooling, ... Unique polymorphs of drug crystal forms with improved pharmaceutical properties can be obtained by ... physical variation (i.e., temperature"). In addition, Galakatos et al. disclose analyzing the

processed array of samples to detect crystalline solid formation and using the results of said measurements to group similar crystalline salt polymorphs (e.g., see Galakatos et al., figures 2 showing a "... schematic of a process to formulate and analyze multiple samples"; see also page 17, last paragraph, "Unique polymorphs of drug crystal forms with improved pharmaceutical properties can be obtained [i.e., grouped into a family with improved characteristics]"; see also page, "Variants of crystallinity can be detected using standard techniques such as solid state spectroscopy, including infrared, Raman, NMR, in a microarray format, or crystallography, x-ray, neutron diffraction, powder x-ray diffraction, light microscopy [i.e., visual analysis], electron microscopy, differential scanning calorimetry, thermal gravimetric analysis, and combinations thereof.").

For ***claim 181***, Galakatos et al. disclose "further analysis" (e.g., see page 21, last two lines, "sample is processed using an UV-VIS HPLC ... and/or passed through another manifold for further analysis for example by HPLC").

For ***claims 188 and 229***, Galakatos et al. disclose less than 1 milligram (e.g., see claim 16, "... test array comprises formulations ... in the range of 1000 micrograms [i.e., 1 milligram] or less in each reservoir or sample site").

For ***claims 189 and 286***, Galakatos et al. disclose Raman spectroscopy (e.g., see page 19, paragraph 1, "Variants of crystallinity can be detected using ... Raman").

For ***claims 190 and 192***, Galakatos et al. disclose quenching of the crystallization process by removing solvent from the samples (e.g., see page, 17, lines 18-20, "Crystallinity variants can be produced by changing crystallization, desolvation, solvent vapor, freeze drying, heating, melting, milling, precipitation, quench cooling, slurry

conversion, spray drying, solid dispersion, and wet granulation; see also pages 15-16, section F, "Exemplary variables involved in processing conditions include selection of the formulation process (freeze drying, dialysis, rate of stirring of drug or carrier in solvent, selection of pH or salt concentrations ...").

For ***claim 191***, Galakatos et al. disclose high throughput screening of all solvents that would include both co-solvents and non-solvents (e.g., see pages 15-16, section F, "the high throughput formulating techniques and screening assays can also be used to compare the efficacy of various formulation conditions, for example, the effects of different solvent").

For ***claim 198***, Galakatos et al. do not explicitly state that their samples contain a group consisting of a) samples containing no precipitate; b) samples with a single polymorph; c) samples with a polymorph mixture; d) samples with amorphous forms or e) samples with mixtures of categories of b-d. However, the Examiner contends that this would be an inherent feature of Galakatos as they aim to optimize the pharmaceutical properties of particular samples which would lead to at least one of the "all encompassing" categories of polymorphs above (e.g., see, page 18, second paragraph, especially, lines 20-23, "Unique polymorphs of drug crystal forms with improved pharmaceutical properties can be obtained by chemical variations (i. e., co-solvents) or physical variation (i. e., temperature)"). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a

comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

For ***claims 199 and 258***, Galakatos et al. explicitly disclose monitoring additional properties such as bioavailability and/or solubility (e.g., see page, "Once constructed, the libraries are screened using automated screens, for example, testing initially for solubility (for example by optical absorbance), then testing lead candidates for oral absorption and then bioavailability using additional in vitro screening or animal testing").

For ***claim 200***, Galakatos et al. disclose the use of "known" compounds (e.g., see page 5, lines 5-7, "These methods result in formulations with improved oral bioavailability... and can be used to obtain ... regulatory compliance for known compounds using bioequivalent formulations").

For ***claim 204***, Galakatos et al. disclose the use of "different" processing methods for different samples (e.g., see Figure 1, wherein "assay(s)" are used i.e., plural conditions; see also page 21, paragraph 1).

For ***claim 207 and 304***, Galakatos et al. disclose adding "additional" components (e.g., see Summary of Invention, "... another preferred embodiment, the formulation is optimized based on microstructure of the drug, the carrier, or the combination of the two components [i.e., an additional component]").

For ***claim 228***, Galakatos et al. disclose "small" molecule pharmaceuticals (e.g., see Summary of Invention; see also Examples wherein small antifungal antibiotics are disclose with molecular weight < 1000).

For ***claims 180, 230-231 and 302-304***, Galakatos et al. disclose both "milligram" and "nanogram" scale (e.g., see background of the invention, "This invention is generally in the field of methods and systems for developing optimized formulations for ... pharmaceutical formulations"; see also lines bridging pages 5-6, "In a more preferred embodiment, the samples consist of less than 25 micrograms"; see also page, 5, lines 22-25, "As used herein, nanoscale refers to formulations or components thereof being present in individual formulations in nanogram quantities").

For ***claim 232***, Galakatos et al. disclose 100-250 µl samples (e.g., see page 25, lines 14-15, "All the solvents were removed by lyophilization. 200 microliters of water were added to each dried formulation in each well of the filter plates").

For ***claim 234***, Galakatos et al. disclose samples that differ from one or more other samples with respect to the amount or concentration of the small molecule pharmaceutical (e.g., see page 6, lines 18-20, "As used herein, compositions refer to mixtures of two or more components or to a library in which one or more variable such as concentration of one or more component is varied").

For ***claims 180, 235, 246, and 302-304***, Galakatos et al. disclose samples that differ from one or more other samples with respect to the identity of one or more of a solvents and/or base (e.g., see pages 15-16, section F, "the high throughput formulating techniques and screening assays can also be used to compare the efficacy of various formulation conditions, for example, the effects of different solvents, pH [i.e., base] ..."; see also page, "For example, component drug, and variations thereof (which can be drug in different amounts, different pHs, different chemical forms such as salts or bases,

different excipients, etc), are distributed in a liquid, gaseous, or dry phase, or combination thereof, into individual test wells or at separate sites in an array").

For ***claim 249***, Galakatos et al. disclose an additive that affects polymorphic form (e.g., see page 18, lines 20-23, "Unique polymorphs of drug crystal forms with improved pharmaceutical properties can be obtained by chemical variations (i. e., co-solvents) [i.e., additives] or physical variation (i. e., temperature)").

For ***claim 295***, Galakatos et al. disclose a solvates (e.g., see Summary of Invention, "Microstructure includes crystalline or amorphous structures, or combinations thereof, polymorphs, solvates").

For ***claim 300***, Galakatos et al. disclose the use of data to identify occurrence of conditions that define occurrence domains that will give rise to a specific crystal form (e.g., page 23, paragraph 1, "There are basically two types of Informatics that can be used ... referring to automated solid or liquid dispensing system and data output, respectively. One is system automation and control software that enables the integrated set of manipulations to occur and track the process flow ... A second is scientific derivatization which collects and stores data to enable further development and design of formulations, including identification of complex interactions between the actives and excipients ... The data can then be processed so as to optimize the ability of scientific personnel to conduct future experiments to optimize the formulations").

For ***claim 301***, Galakatos et al. disclose machine vision technology (e.g., see page, "Variants of crystallinity can be detected using ... light microscopy" wherein the

machine is the microscope that uses "visual" analysis; see also 35 U.S.C. 112, second paragraph rejection above).

The prior art teachings of Galakatos et al. differ from the claimed invention as follows:

For ***claims 180, 186 and 302-304***, Galakatos et al. fail to disclose a worklist.

For ***claims 180, 299, 302-304***, Galakatos et al. fail to disclose a "modular" design for automation.

For ***claims 180, 184 and 302-304***, Galakatos et al. fail to describe method steps for "sealing" the samples.

For ***claims 180, 182-184, 302-304***, Galakatos et al. disclose support plates, but fail to disclose "tubes" in said support plates (e.g., see Example 2).

For ***claim 183***, Galakatos et al. fail to disclose "metal" support plates and/or "glass" vials.

For ***claim 187, 193 and 233***, Galakatos fail to disclose "septum-piercing" capabilities with or without the use of aspiration.

For ***claim 299***, Galakatos fail to disclose incubation and detection "modules."

However, Merritt, Saneii et al., Newsam et al. and Wang et al. teach the following limitations that are deficient in Galakatos et al.:

For ***claims 180, 186 and 302-304***, the combined teachings of Merritt, Saneii et al., Newsam et al. and Wang et al. disclose the use of a work-list such as an Excel™ spread sheet that is used as a work list to "automatically convert a test file containing relevant information about the microtiter plate synthesis into a format amendable to automated

data acquisition and data processing" (e.g., see Wang et al., entire document, especially Table 1).

For ***claims 180, 299, 302-304***, the combined teachings of Merritt, Saneii et al., Newsam et al. and Wang et al. disclose a "modular" design for automation (e.g., see Merritt, page 507, column 2, last paragraph, "... instead of developing a single piece of equipment to perform all the function for the synthetic process we had separated the functions into stand-alone modules. This allowed more-flexible equipment scheduling and use").

For ***claim 180, 184 and 302-304***, the combined teachings of Merritt, Saneii et al., Newsam et al. and Wang et al. (see entire document) teach the use of "sealing" the samples, for example, with "self sealing septums" (e.g., see column 3, lines 36-38, "The mouth 31 of each of the wells 30 is sealed by a self sealing septum (not shown) penetratable by the probe 26 as is well understood in the art"; see also figures 1-6; see also Merritt, page 506, column 1, last paragraph wherein the "Tecan" robotic sampler is disclosed).

For ***claim 180, 182-184 and 302-304***, the combined teachings of Merritt, Saneii et al., Newsam et al. and Wang et al. teach the use of tubes in support plates (e.g., see Merritt, figure 1).

For ***claim 183***, the combined teachings of Merritt, Saneii et al., Newsam et al. and Wang et al. teach the use of metal support plates such as aluminum (e.g., see column 4, paragraph 2, "The manifold 38 also serves as the temperature control means for controlling the reaction temperature in the reaction wells 30. Accordingly it is preferred

that the reaction block 30, or at least the lower portion defining the manifold 38 be formed from a thermally conductive material, such as an aluminum alloy"; see also figure 4, element 30). The combined teachings of Merritt, Saneii et al., Newsam et al. and Wang et al. also teach the use of glass vials (e.g., see Newsam et al., page 208, column 1, paragraph 3, "Lapointe used a robotic liquid dispenser in a glove box to load the reagents into an array of 1-mL glass vials which were sealed and shaken at room temperature over night").

For ***claims 187, 193 and 233***, Galakatos disclose septum-piercing capabilities (e.g., see column 3, lines 36-38, "The mouth 31 of each of the wells 30 is sealed by a self sealing septum (not shown) penetratable by the probe 26 as is well understood in the art"; see also figures 1-6; see also figure 1, especially element 26; see also examples).

It would have been obvious to one skilled in the art at the time the invention was made to use any of the large number of commercially available robotic liquid handling devices such as those disclosed by the combined teachings of Merritt, Saneii et al., Newsam et al. and Wang et al. to prepare and/or analyze the combinatorial pharmaceutical formulations disclosed by Galakatos et al. because the commercially available liquid handling devises disclosed by the combined teachings of Merritt, Saneii et al., Newsam et al. and Wang et al. were explicitly designed for this purpose (e.g., see Merritt, column 1, paragraph 1, "The introduction of automation and the increasing levels of miniaturization in the high-throughput screening (HTS) arena at the start of the 1990s [i.e., ~10 years before the filing date of the present application] provided the impetus for the development of combinatorial chemistry in drug discovery"; see also page 510,

column 1, paragraph 1, "These techniques [automated HTS] have been embraced by medicinal chemists, and are now applied as part of the wide range of approaches available to tackle the discovery and development of new drugs"; compare with Galakatos et al., abstract, "In a preferred application, the bioavailability and pharmacokinetics [i.e., development] of the drugs, especially small molecule pharmaceuticals, are optimized"). Furthermore, one of ordinary skill in the art would have been motivated to use the commercially available liquid handling devices as disclosed by the combined teachings of Merritt, Saneii et al., Newsam et al. and Wang et al. because according to Merritt, Saneii et al., Newsam et al. and Wang et al. these automated systems have numerous advantages for conveniently and reproducibly screening large numbers of samples with optimal controls by the practitioner to increase the speed and/or reduce the costs via, for example, the use of smaller sample volumes and fast "robotic" automation and/or computer generated work-lists (see Merritt page 507, column 2, last paragraph, "... instead of developing a single piece of equipment to perform all the functions for the synthetic process we had separated the functions into stand-alone modules. This allowed more-flexible equipment scheduling and use"; see also Wang et al., paragraph bridging pages 1125-1126, "Our ease of acquiring FIA-MS data on samples 8 in a time of less than one minute suggested the possibility of processing an entire microtiter plate in less than 10 minutes (providing at least a four- to five-fold speed advantage over existing technologies). However, to maintain this speed advantage, it was critical to develop tools to facilitate automated data acquisition and data processing ... To permit autosampling of eight samples at a time, an Excel™ macro was

used to automatically convert a text file, containing information about the expected products in each well of the microtiter plate, into a format amenable to automated data acquisition and data processing of eight samples at a time"; and Saneii et al., last two paragraphs, "Reproducability and reliability of the synthesis is insured by elimination of manual manipulation once the protocol has been properly entered into the controller"). Finally, one of ordinary skill in the art would have reasonably expected to be successful because the combined teachings of Merritt, Saneii et al., Newsam et al. and Wang et al. disclose automated robotic liquid sample handlers have chemical compatibility with a wide range of solvents and/or reagents and had been employed to speed up and reduced costs in every conceivable area of chemistry including catalysts, pharmaceuticals, polymers, etc using every conceivable detection means e.g., NMR, MS/MS, Raman, etc (e.g, see Saneii et al., last two paragraphs, "From the foregoing it will be seen that the apparatus of the present invention is highly flexible and is capable of synthesizing a variety of compounds in a single setup or producing a larger quantity of a single compound in the wells").

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
March 21, 2005